CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DIIODOMETHYL-P-TOLYL SULFONE

Chemical Code # 2150, Tolerance # 50307
SB 950 # 644

January 11, 2006

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file.
Chronic toxicity, dog:	Data gap, no study on file[1].
Oncogenicity, rat:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	Data gap, inadequate study, possible adverse effect indicated.
Teratology, rabbit:	Data gap, inadequate study, possible adverse effect indicated.
Gene mutation:	Data gap, inadequate study, no adverse effect.
Chromosome effects:	Data gap, inadequate study, no adverse effect.
DNA damage:	Data gap, inadequate study, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 126528 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: t060111.doc
Prepared by J, Kishiyama and S. Morris, January 11, 2006

1. A possible adverse effect was identified in a three-month subchronic feeding study in dogs (see DPR doc. # 50307-024, rec. # 126528).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study on file.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

50307-005; 042933; "Evaluation of the Effects of Orally Administered Abbott-9248 (Amical 48) on the Embryonic and Fetal Development of the Rat (Seg. II, TFR)," Study No. TA85-022; S.B. Lehrer; Abbott Laboratories, Abbott Park, IL; October 8, 1985. Groups of 22 sperm-positive mated female Sprague-Dawley-derived (Crl:CD® (SD) BR) rats/dose were given Diiodomethyl-P-Tolyl Sulfone (Abbott-9248, lot #66-207-CB, purity not stated, suspended in 0.2% hydroxypropylmethylcellulose, lot #113-02) by oral gavage at 0, 100, 300, or 1,000 mg/kg/day on gestation days 6 through15. All surviving rats were killed on gestation day 20, fetuses were delivered by abdominal section and uteri and fetuses examined for reproductive and developmental effects. Treatment-related maternal effects included clinical signs (no data), decreased food consumption and body weight gain at 1,000 mg/kg/day (maternal NOEL = 300 mg/kg/day). Treatment-related fetal effects included slightly (4%, NS) decreased weight and umbilical hernias (2.1% versus 0% in control fetuses) at 1,000 mg/kg/day (developmental NOEL = 300 mg/kg/day). A **possible adverse effect** was indicated the by the developmental NOEL = maternal NOEL. The study was unacceptable but possibly upgradeable with submission of adequate data for test article purity and stability, dosing material homogeneity and stability, maternal necropsy, corpora lutea, individual maternal, fetal and litter data. Independent evaluation cannot be made based on insufficient information presented (J. Kishiyama and S. Morris, 1/10/05).

50307-005; 042934; "Evaluation of the Effects of Orally Administered Abbott-9248 on the Development of the Rat Fetus, a Partial Repeat of Study No. TA85-022," Study No. TA85-230; S.B. Lehrer; Abbott Laboratories, Abbott Park, IL; 1/22/86. Groups of 25 sperm-positive mated female Sprague-Dawley-derived (Crl:CD®(SD)BR) rats/dose were given Diiodomethyl-P-Tolyl Sulfone (Abbott-9248, lot #66-207-CB, purity not stated, suspended in 0.2% hydroxypropylmethylcellulose, lot #113-02) by oral gavage at 0, or 1,000 mg/kg/day on gestation days 6 through15. All surviving rats were killed on gestation day 20, fetuses were delivered by

abdominal section and uteri and fetuses examined for reproductive and developmental effects. Treatment-related maternal effects included decreased food consumption and body weight gain and lethality (3) at 1,000 mg/kg/day (maternal NOEL not determined). There were no treatment-related developmental effects (developmental NOEL ≥ 1,000 mg/kg/day). No adverse effect was indicated. The study was unacceptable and not upgradeable because there was only one treatment group and inadequate data for test article purity and stability, dosing material content, homogeneity and stability, maternal necropsy, corpora lutea, individual adults, fetuses and litters. This study was a partial repeat of "Evaluation of the Effects of Orally Administered Abbott-9248 (Amical 48) on the Embryonic and Fetal Development of the Rat (Seg. II, FR)," Study No.TA85-022; S.B. Lehrer; Abbott Laboratories, Abbott Park, IL; October 8, 1985 (DPR doc. # 50307-005 rec. # 042933) to investigate a possible developmental treatment effect on the frequency of fetal umbilical hernias. The combined data of the two studies does not fill the data gap. The registrant should submit the data requested for Study No.TA85-022 or perform a replacement study (J. Kishiyama and S. Morris, 1/18/05).

TERATOLOGY, RABBIT

50307-005; 042935; "Evaluation of the Effects of Orally Administered Abbott-9248 on the Embryonic and Fetal Development of the Rabbit - Segment II TFR," Study No. TE85-054; S.B. Lehrer; Abbott Laboratories, Abbott Park, IL; December 17, 1985. Groups of 16 mated female New Zealand White rabbits/dose were given Diiodomethyl-P-Tolyl Sulfone (Abbott-9248, lot #66-207-CB, purity not stated, suspended in 0.2% hydroxypropylmethylcellulose, lot #113-02) by oral gavage at 0, 4, 15, or 60 mg/kg/day on gestation days 6 through18. All surviving animals were killed on gestation day 29, fetuses were delivered by abdominal section and uteri and fetuses examined for reproductive and developmental effects. Corpora lutea were counted. Treatment-related maternal effects included deaths (11/16) at 60 mg/kg/day, abortions at 0, 4, 5 and 60 mg/kg/day (3, 1, 2 and 5) and decreased food consumption and body weight gain at 15 and 60 mg/kg/day (maternal NOEL =4 mg/kg/day). A **possible adverse effect** was indicated by treatment-related developmental effects that included decreased viable fetuses and increased degenerating fetuses (late embryonic death) at 15 and 60 mg/kg/day and gnarled forepaws and hydrocephalus at 15 mg/kg/day (developmental NOEL = 4 mg/kg/day). The study is unacceptable and not upgradeable because of inadequate number of control animals, analysis of the test article and dosing material not reported, the starting age and weight of the animals were not given, excessive mortality, too few surviving dams, no individual maternal or litter data, and no GLP sign-off (J. Kishiyama and S. Morris, 1/20/05).

GENE MUTATION

50307-005; 042930; "Mutagenicity Evaluation of A-47685 Lot 5935-70 Final Report," LBI Project No. 2683; D.J. Brusick; Litton Bionetics, Inc.; February, 1977. The plate incorporation method was used to evaluate the mutagenic potential of Diiodo-p-tolyl sulfone (A-47685, Lot 5935-70, purity not stated, colorless liquid, DMSO solvent) using histidine auxotrophic strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and *Saccharomyces cerevisiae* (D4). Single samples of approximately 10^8 cells were exposed to the test material at 0 (DMSO), 0.001, 0.01, 0.1, 1.0 and 5.0 μl/plate with and without S9 metabolic activation system (9,000 g supernatant of liver homogenates from Aroclor 1254-induced, male Sprague-Dawely rats), grown up for 48 hours in minimal media and scored for colonies of prototrophic (revertant) bacteria. Treatment-related increases in revertant colonies or cytotoxicity were not seen with or without S9. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material, only one replicate/dose/strain, no repeat trial and lack of protocol details (J. Kishiyama and S. Morris, 1/4/05).

50307-005; 042931; "Mutagenicity Evaluation of A-47685 50/50 Mixture with Dipropylene Glycol, Lot #1, Final Report," LBI Project No. 2683; D.J. Brusick; Litton Bionetics, Inc.; February 1977. The plate incorporation method was used to evaluate the mutagenic potential of a 50:50 mixture (Lot 1) of Diiodo-p-tolyl sulfone (A-47685, yellow liquid, purity and lot number not stated) and Dipropylene Glycol (purity and lot number not stated) using histidine auxotrophic strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and *Saccharomyces cerevisiae* (D4). Single samples of approximately 10^8 cells were exposed to the test material at 0 (DMSO solvent)), 0.001, 0.01, 0.1, 1.0 and 5.0 μl/plate with and without S9 metabolic activation system (9,000 g supernatant of liver homogenates from Aroclor 1254-induced, male Sprague-Dawely rats), grown up for 48 hours in minimal media and scored for colonies of prototrophic (revertant) bacteria. Treatment-related increases in revertant colonies or cytotoxicity were not seen with or without S9. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material, the pure active ingredient was not used, only one replicate/dose/strain, no repeat trial, no rationale for the doses and lack of protocol details (J. Kishiyama and S. Morris, 1/4/05).

50307-005; 042932**;** "Mutagenicity of A-9248 in a Mouse Lymphoma Mutation Assay, Final Report," LBI Project No. 20989; M.A. Cifone; Litton Bionetics, Inc.; December 1985. Diiodomethyl-P-Tolyl Sulfone (A-9248, lot # 66-207-CB, mustard yellow powder, purity not stated, DMSO solvent) was evaluated for the ability to induce forward mutations in the thymidine kinase loci (TK) of cultured mouse lymphomas cells (L5178Y) from TK +/- to TK -/-. TK -/- mutants were selected by their immunity to the lethal affects 5-trifluorothymidine (TFT) have on TK +/-. Single samples of approximately $6X10^6$ logarithmically growing cells were incubated for 4 hours in medium containing the test material at 0.0, 0.5, 1.0, 2.0, 3.0, 4.0 or 5.0 with S9 metabolic activation system (9,000 g supernatant of liver homogenates from Aroclor 1254-induced, male rats) or 0.0, 0.3, 0.5, 0.6, 0.8,1.0 or 2.0 μg/ml without S9. The cells were then washed twice, reseeded in fresh medium and incubated 2 days with cell count adjusted day 1. Samples of approximately $3X10^6$ cells were incubated in selection media (3 μg/ml TFT, other conditions not defined). Each sample was then plated in triplicate at approximately $1X10^6$ cells/100 mm dish, incubated for 10 to 14 days and scored for mutant (TFT resistant) colonies. Colony counts were combined for the 3 dishes/dose. Cloning efficiency was also determined. There were no treatment-related effects on mutation rate. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material and there was only one trial with one sample/dose (J. Kishiyama and S. Morris, 1/7/05).

CHROMOSOME EFFECTS

50307-008; 044532; "Clastogenic Evaluation of A-9248 Lot #66-207-CB in the In Vivo Mouse Micronucleus Assay, Final Report," HB Project No.: 20895; J.L. Ivett; Hazleton Biotechnologies, Kensington, MD; January 1986. Three groups of 5 ICR mice/sex were dosed ip with Diiodomethyl-P-Tolyl Sulfone (A-9248 Lot #66-207-CB, beiger powder, purity not stated) at 0.0 (corn oil, 10 ml/kg), 0.5, 2.5, or 5.0 g/kg and sacrificed 24, 48, or 72 hours. Tibia bone marrow was harvested, spread on slides, fixed and stained. One thousand polychromatic erythrocytes were microscopically scored for micronuclei and the ratio of polychromatic erythrocytes to erythrocytes was determined. No treatment-related effects were reported. Treatment-related increases in micronuclei were not seen (NOEL ≥ 5.0 g/kg). No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analysis of the test article and content stability and homogeneity of the dosing material (J. Kishiyama and S. Morris, 2/1/05).

DNA DAMAGE

50307-008; 044533; "Evaluation of A-9248 in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay," LBI Project No. 20991; M.A. Cifone; Litton Bionetics, Inc., LBI; December

1985. Primary hepatocytes were obtained by in situ collengenase profusion of male Fischer 344 rat livers. Monolayer cultures were established on plastic coverslips and used the same day to measure unscheduled DNA synthesis (UDS). Five monolayer cultures/dose were exposed to media containing Diiodomethyl-P-Tolyl Sulfone (A-9248, lot No. 66-207-CB, purity not stated) at 0.0 (1% DMSO), 0.052, 0.104, 0.259, 1.04, 3.89, 5.19 or 10.4 μg/ml plus ^{3}H-thymidine at 1 μCi/ml for 18 to 19 hours. Two cultures/dose were washed, refed media, incubated 20 – 24 hours and assessed for viability using by trypan blue exclusion. The remaining 3 cultures/dose had their nuclei swollen, fixed and air dried. Autoradiographic analysis of ^{3}H was performed by mounting the coverslips, coating them with photographic emulsion and allowing for 7-10 days for exposure.

Emulsions were then developed and nuclear material fixed and stained. UDS was measured by microscopically determining the net (nuclear – cytoplasmic) ^{3}H grain counts of 50 nuclei / culture (150 / dose). Treatment-related decreases in viability were seen at 3.89, 5.19 and10.4 μg/ml. No treatment-related effect on UDS was seen. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with adequate subsmissions of purity and stability of the test material and cytoplasmic and nuclear grain counts for individual cultures (J. Kishiyama and S. Morris, 2/2/05).

SUBCHRONIC STUDIES

50307-022;126526; "21-Day Subacute Dermal Toxicity in the Rabbit," PRL Report No.: 7820; A.S. Tegeris; Pharmacopathics Research Laboratories, Inc., Laurel, MD; 4/9/79. Groups of 3 New Zealand albino rabbits/sex were exposed on areas of intact or abraded skin to Diiodomethyl-P-Tolyl Sulfone (ABB -9248, lot # 80-851-CA, light yellow dry powder, purity 95-100%) at 0 (water), 200, 600, or 2000 mg/kg/day for 21consecutive days, 4hours per day, followed by a 14-day observation period. Treatment-related effects included: erythema with intact and abraded skin in both sexes at 200, 600 and 2,000 mg/kg/day; mortality with intact skin in males at 600 mg/k/g/day and both sexes at 2,000 mg/k/g/day; mortality with abraded skin in males at 200 mg/k/g/day and both sexes at 600 and 2,000 mg/k/g/day; decreased body weight gain for intact and abraded skin in females at 600 and 2,000 mg/k/g/day; hyperkeratosis for intact and abraded skin in both sexes at 600 and 2,000 mg/k/g/day and abraded males at 200 mg/kg/day and zonal hepatic atrophy and fatty infiltration of the liver for intact and abraded skin in both sexes at 600 and 2,000 mg/k/g/day (NOEL< 200 mg/k/g/day). No adverse systemic effect was indicated. The study was unacceptable and not upgradeable because there were no analyses of the stability of the test article or dosing materials; mortality was seen at all doses; only 3 rabbits/sex/dose were used; clotting time was not measured; serum electrolytes were not measured; abraded skin was used; exposure was only 4 hours / day; a recovery period was used and there were no GLP and/or QA sign-offs. (J. Kishiyama and S. Morris, 2/7/05).

50307-023; 126527;AThree-Month Toxicity Study of Amical7 48 Administered Via the Diet to Rats,@ Laboratory Project ID TA85-096; R.E. Dudley; Abbott Laboratories, North Chicago, IL; February 14, 1986. Groups of 10 Crl:CD7(SD)BR rats/sex were fed dietary mixtures of Diiodomethyl-P-Tolyl Sulfone (Amical7, Abbott-9248; lot #68-332-CB, 94.3 - 95.9% stated purity) for 90 days at nominal doses of 0, 5, 20, or 80 mg/kg/day (actual = 100.41 – 108.23% of nominal). There were no treatment-related effects on mortality, clinical signs, food consumption, clinical pathology, ophthalmology, organ weights or gross pathology. Salivatory gland ductal squamous metaplasia was seen at 80 mg/kg/day (NOEL = 20 mg/kg/day). No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of an adequate rationale for the doses used (J. Kishiyama and S. Morris, 2/18/05).

50307-024; 126528; AThree-Month Toxicity Study of Amical7 48 Administered Orally to Dogs," Laboratory Project IDTB85-158; J.M. Creighton; Abbott Laboratories, North Chicago, IL; 2/13/86. Groups of 4 Beagle dogs/sex were dosed orally for 96 to 100 days with Diiodomethyl-P-Tolyl Sulfone (Amical7 48, ABBOTT-9248, Lot # 68-332-CB, purity not stated) in gelatin capsules at 0,

2, 10 or 60 mg/kg/day. Treatment-related effects included eye discharge, abnormal feces, decreased body weight gain, salivary gland sialadenitis, increased white cell count and decreased serum albumin in both sexes at 60 mg/kg/day. A **possible adverse effect** was indicated by thyroid degeneration in both sexes at 10 and 60 mg/kg/day (NOEL= 2 mg/kg/day). The study was unacceptable but possibly upgradeable with adequate submissions of analytical data for the test a
rticle and dosing material and rationale for the doses used (J. Kishiyama and S. Morris, 2/28/05).

These records have been reviewed.

50307-005	042930
50307-005	042931
50307-005	042932
50307-005	042933
50307-005	042934
50307-005	042935
50307-008	044532
50307-008	044533
50307-022	126526
50307-023	126527
50307-024	126528